Clinical Pharmacology Of Malaria

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SUMMARY

Effective chemotherapy of malaria relies on an accurate diagnosis and an appropriate affordable choice of drugs bearing in mind likely adverse effects, patterns of drug resistance, and the degree of host immunity.

Choice of Antimalarial Drug: Treatment of multidrug-resistant *Plasmodium falciparum* malaria prevalent in our environment relies increasingly on combination chemotherapy using blood schizonticides. Chloroquine and Sulfodoxine/Pyremethamine have been cheap and safe options. However widespread resistance to these drugs (and the problem of chloroquine-related pruritus) means that these agents are often ineffective. Quinine has been relied on for multidrug-resistant malaria. However its marked toxicity potential (e.g. cinchonism and ventricular tachyarrhythmias) means that other drugs such as mefloquine, doxycycline, chlorproguanil-dapsone and proguanil-atovaquone are preferred. Halofantrine is not recommended because of its cardiotoxic potential. Increasing problems with drug resistance have led to current recommendations for the use of artemisinin-based combination therapy such as co-artemether (artemether plus lumefantrine). *Plasmodium vivax, P. ovale* and *P. malariae* remain sensitive to chloroquine, and likewise the emergent parasite *P. knowlesi.* Primaquine is used to eradicate hypnozoites of *P. vivax* and *P. ovale.*

Treatment of malaria: Prompt treatment is of vital importance, especially in patients who lack innate or acquired immunity. Delaying effective treatment increases morbidity and mortality. Circumstances such as pregnancy and infancy should be taken into account, for example to avoid possible teratogenic effects of mefloquine, artemisinins or halofantrine during the first trimester, and to avoid primaquine and halofantrine while breastfeeding. Supportive treatment is important in severe malaria. Fever is part of the host defence against infection and so should not be entirely suppressed. Careful attention should be paid to fluid balance, to postural hypotension and hypoglycemia (which are exacerbated by quinoline antimalarials), to accompanying bacterial infections, renal impairment and the need for anticonvulsants or blood transfusion.

Therapeutic failure may be due to a wrong diagnosis, or an additional cause for the febrile illness apart from malaria. Parasite resistance to antimalarials, poor patient compliance, and the use of fake or substandard drugs are alternative explanations.

Key Words: *Malaria, Drug treatment of Malaria, Clinical Pharmacology*

INTRODUCTION

The optimal treatment for malaria relies on an accurate diagnosis in the first instance. A high index of suspicion is required not to miss cases, especially in febrile patients, even if an alternative explanation for pyrexia is apparent. Checking for malaria parasitaemia is a simple procedure which should be undertaken if there is any likelihood of malaria contributing to a patient's presentation.

Choosing the optimal drug treatment for a case of malaria is a complex decision which

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should take account not only of the causative species and the local pattern of drug resistance, but also the degree of host immunity, host drug intolerance, drug-related factors (such as affordability, availability, quality and reliability), special circumstances such as pregnancy, and the presence of serious complications of severe malaria such as cerebral involvement and hypoglycaemia. This review will discuss the individual antimalarial drugs available before considering their optimal usage in the treatment of malaria. An old adage states that 'prevention is better than cure'. However preventive measures such as avoiding mosquito bites (long-sleeve clothing, impregnated bed nets) and prophylactic chemotherapy fall outside the scope of this article. Ironically with malaria, cure may be better than prevention insofar as occasional attacks help to maintain some immunity without which the patient would be at risk of severe complicated malaria.

PHARMACOLOGY OF ANTIMALARIAL DRUGS

Antimalarial drugs may be conveniently classified according to the stage of the malaria parasite life-cycle at which they exert their main action (see table 1).

Table 1 Classification of Antimalarial Drugs[a]

TISSUE SCHIZONTICIDES			BLOOD SCHIZONTICIDES				
8-Aminoquinolines	**Antifolates**	**4-Aminoquinolines**	**Quinolines**	**Antifolates and Atovaquone[b]**	**Artemisinin derivatives**	**Leaf Extracts**	**Antibacterials**
Priamquine	Proguanil	Chloroquine	Quinine	P-S	Artesunate	Irab[c]	Tetracycline
Tafenoquine	Pyremethamine	Amodiaquine	Quinidine	C-D	artemether		Doxycycline
			Mefloquine	P-A			Clindamycin
			Halofantrine				Azithromycin
			Lumefantrine				Fluoroquinolones

[a]Tissue schizonticides may be used for casual prophylaxis (i.e. preventing pre-erythrocytic shchizogony) of all forms of malaria and to prevent relapse from exo-erythrocytic schizogony, as occurs with *Plasmodium vivax* and *P. ovale*. Blood schizonticides are useful in the treatment of acute attacks of malaria i.e. they are effective against erythrocytic schizogony.
[b](P-S: Pyremethamine-Sulfadoxine; C-D: Chlorproguanil-Dapsone; P-A: Proguanil-Atovaquone)
[c]Neem leaf extract

CHLOROQUINE

Chloroquine remains the most widely used antimalarial in spite of widespread resistance of *Plasmodium falciparum* to the drug. Chloroquine is still the drug of choice for *Plasmodium vivax, ovale* and *malariae* infections.

Pharmacokinetics: chloroquine is given by oral administration at a dosage of 10 mg/kg (base), then 5 mg/kg after 6 hours, then 5 mg/kg daily for two days. The intramuscular dose is 3 mg/kg daily for 3 days. The drug is rapidly and completely absorbed from the gastrointestinal tract. It is about 60% protein-bound. It is rapidly and widely distributed and concentrated in tissues, with a volume of distribution of about 13,000 litres in the adult. Chloroquine is eliminated by renal excretion with a half-life of about 4 days.

Pharmacodynamics: the mode of action is uncertain. Chloroquine is highly concentrated in parasitised erythrocytes. Resistance to chloroquine is mediated by a membrane P-glycoprotein pump which expels chloroquine from the parasite.

Toxicity: adverse effects include rashes, pruritus, gastrointestinal symptoms, headaches, visual disturbance and convulsions. Prolonged

high dosage eventuates in retinopathy. Rapid intravenous administration must be avoided as this may lead to severe hypotension. Chloroquine is contraindicated in psoriasis, porphyria and retinal abnormality as it may make these disorders worse.

MEFLOQUINE

Mefloquine was developed in the quest to tackle chloroquine-resistant *Plasmodium falciparum* malaria[1].

Pharmacokinetics: Mefloquine is administered orally at a dosage of 20-25 mg/kg (base) preferably as 2-3 divided doses 6-8 hours apart. It is well absorbed after oral administration, highly protein-bound and extensively distributed with an elimination half-life of about 24 hours.

Pharmacodynamics: Its mode of action is uncertain. Mefloquine is particularly effective against multidrug-resistant *Plasmodium falciparum* malaria. However resistance to mefloquine has been reported from Thailand.[2]

Toxicity/ contraindications: Side effects of mefloquine include vomiting, dizziness, drowsiness, dysphoria and nightmares. Mefloquine may aggravate epilepsy and neuropsychiatric disorders. Hence it should not be given to patients with these conditions. Mefloquine may also predispose to arrhythmias by prolonging the QT-interval, and hence should not be combined with drugs such as quinine, quinidine and halofantrine.

SULFADOXINE AND PYRIMETHAMINE

Pharmacokinetics: The two component drugs of this combined preparation are well absorbed after oral administration as a single dose of three tablets each containing 500 mg sulfadoxine and 25 mg pyrimethamine. They reach peak plasma levels within 2-8 hours and are excreted mainly by the kidneys. The half-lives are about 170 hours for sulfadoxine and 100 hours for pyrimethamine.

Pharmacodynamics/ clinical use: Pyrimethamine may be used alone for the prevention of malaria, but is inadequate for treatment. Indeed resistance and failure of prophylaxis are common. Combining the sequential antifolate actions of a long-acting sulphonamide (inhibition of folic acid synthesis) and pyrimethamine (inhibition of Plasmodial dihydrofolate reductase) results in therapeutically useful antimalarial activity. Single-dose treatment with sulfadoxine-pyrimethamine (S-P), or similar alternatives such as dapsone-pyrimethamine, has been effective in areas with chloroquine resistance such as most of Africa, South America and parts of Asia. S-P action is slow: it usually takes up to 3 days for malaria to resolve clinically. Unfortunately resistance to S-P has developed rapidly in many areas, particularly South America and Southeast Asia. A combination preparation incorporating S-P and mefloquine, although relatively expensive, is useful where resistance to S-P is a problem.

Toxicity: Another disadvantage is that S-P has the potential for serious toxicity, especially with repeated use: for example exfoliative dermatitis, hepatitis and blood dyscrasias may occur.

AMODIAQUINE

Amodiaquine is structurally similar to chloroquine with similar pharmacokinetic and pharmacodynamic properties. The oral dosage is 600 mg stat. It retains antimalarial activity where there is low-grade resistance to chloroquine[3]. However amodiaquine is metabolised to a toxic quinone-imine such that repeated use of the drug entails the risk of hepatitis and possibly fatal agranulocytosis[3].

QUININE AND QUINIDINE

Quinine is derived from the bark of the cinchona tree and has been used in antimalarial treatment and prophylaxis for over three centuries.

Pharmacokinetics: The oral dosage is 10 mg/kg salt 8 hourly for 7 days. Quinine is rapidly absorbed after oral administration and is about 80% protein-bound with an elimination half-life of 8-21 hours. 80% is metabolised in the liver and the remainder excreted in the urine.

Pharmacodynamics: Although its mode of action is unclear, it generally depresses enzyme systems and blocks DNA transcription in the parasite. Resistance has been reported from Southeast Asia; in such cases the course of quinine should be followed either by S-P 3 tablets stat, or doxycycline 200 mg daily for a week.

Toxicity/ precautions: Side effects include gastric irritation causing emesis, a curare-like effect on skeletal muscle and stimulation of insulin release causing hypoglycaemia. Cinchonism comprises headache, emesis, visual disturbance, dizziness, tinnitus and dysphoria. If severe, blindness and deafness may result. Quinine may also cause fever, rashes, haemolysis and hemoglobinuria (blackwater fever). The drug is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency. Quinine depresses cardiac conduction, prolonging the PR and QT intervals. This predisposes to heart block and dangerous ventricular tachyarrhythmias. Rapid intravenous administration must be avoided as this may lead to severe hypotension, seizures, ventricular fibrillation and death. The dextrorotatory stereoisomer of quinine, quinidine, has greater antimalarial efficacy than quinine, but also greater cardiotoxicity, such that electrocardiographic monitoring is required if it is to be used[4].

DOXYCYCLINE AND OTHER ANTIBACTERIAL AGENTS

Doxycycline, tetracycline and sulphonamides have slow antimalarial activity as blood schizonticides. Less frequently used slow-acting schizonticides include clindamycin, azithromycin and fluoroquinolones[5]. In view of their slow action, these drugs are mainly useful as part of synergistic combination therapy to combat resistant parasites. Examples include quinine followed by tetracycline (500 mg qds for 7 days) or clindamycin (900 mg tds for 3 days), chloroquine plus doxycycline (100 mg bd for 7 days). The sulfadoxine-pyrimethamine combination has been discussed above. Doxycycline is used on its own as a prophylactic drug (100 mg daily) for up to three months, especially in areas where multidrug resistant *Plasmodium falciparum* is prevalent.

Pharmacokinetics: The oral dosage of tetracycline is 500 mg six hourly, its serum half-life being 6-8 hours. Doxycycline is more lipid soluble and hence better absorbed with a longer half-life (16-18 hours): the adult dose is 100 mg once or twice a day. Unlike tetracycline, the absorption of doxycycline is not significantly affected by food. Tetracyclines in general chelate with divalent cations, and hence should not be administered with milk, antacids or ferrous sulphate.

Pharmacodynamics: Tetracyclines inhibit protein synthesis by binding reversibly to the 30S ribosomal subunit of susceptible microorganisms.

Adverse effects/ contraindications: Gastrointestinal irritation may result in nausea, vomiting and diarrhoea. Suppression of normal colonic bacterial flora may result in overgrowth of resistant pathogens e.g. *Pseudomonas, Proteus, Candida, Clostridium difficile*. The last of these may cause pseudomembranous colitis.Tetracyclines are incorporated into, and hence may damage, growing bones and teeth. Hence they are contraindicated in pregnancy and below the age of seven years.

HALOFANTRINE

Pharmacokinetics: There is variable absorption of halofantrine after oral administration (3 doses of 500 mg 6-hourly, repeated after a week). This

absorption is increased by administering the drug with fatty foods. Hence the drug should not be taken as from one hour before until 3 hours after meals. The half-life is 4-5 days and excretion mainly in the faeces.

Pharmacodynamics: Halofantrine is a blood schizonticide effective against multidrug resistant *Plasmodium falciparum*. However there have been some reports of resistance to halofantrine[6].

Toxicity: Halofantrine is generally well tolerated, rarely causing abdominal pain, diarrhoea and pruritus. However the drug is no longer recommended for malaria because it may rarely cause life-threatening cardiotoxicity, especially if combined with other drugs which also prolong the PR and QT intervals[7].

ARTEMISININ DERIVATIVES

These are derived from a Chinese herbal remedy which has been used to treat fevers for over 2000 years.

Pharmacokinetics: These include artesunate and artemether which are rapidly absorbed after oral or parenteral administration. The intramuscular dosage of artemether is 3.2 mg/kg on the first day followed by 1.6 mg/kg per day for up to 7 days, or until the patient can take oral drugs. The dosage for artesunate is 2 mg/kg followed by 1 mg/kg per day until the patient can take oral treatment. These drugs are hydrolysed to their active metabolite, dihydroartemisinin, which is widely distributed in the body with an elimination half-life of about four hours.

Pharmacodynamics: The artemisinins are blood schizonticides, effective against all blood stages of *Plasmodium falciparum*, including chloroquine-resistant strains. They exhibit better efficacy and safety than other antimalarials discussed so far. There is faster clearance of parasitemia than with other drugs, and a notable lack of toxicity. No resistance has been reported so far. Artemether has been shown to be superior to quinine in preventing death or adverse neurological sequelae in severe *Plasmodium falciparum* malaria[8 - 10]. Parenteral artemether is a drug of choice in patients with cerebral malaria.

The remarkable efficacy and safety of artemisinins, and the lack of parasite resistance to them, have led to studies of combination chemotherapy, incorporating artemisinins, in an effort to further promote efficacy and forestall the development of resistance. Combining artesunate with mefloquine in Thailand resulted in high cure rates and halted the progression of resistance to mefloquine[2, 11]. In Africa, adding 3 days of artesunate to standard treatments with chloroquine, amodiaquine or S-P, substantially reduced treatment failure, recrudescence, and gametocyte carriage. However success was limited where there were high levels of resistance to the background drug, as for example with chloroquine in West Africa and S-P in East Africa[12]. To address these concerns, a fixed combination of two drugs with established safety and efficacy, viz 20 mg artemether and 120 mg lumefantrine (co-artemether) has recently been developed for the treatment of multidrug resistant *Plasmodium falciparum* malaria. Through WHO, Novartis will supply co-artemether to developing countries at cost because the normal commercial price would be unaffordable[13]. The oral dosage is 4 tablets at 0, 8, 24, 36, 48 and 60 hours.

PRIMAQUINE, TAFENOQUINE

Pharmacokinetics: Primaquine is administered orally at a dose of 250 ug/kg daily for 14 to 21 days. Peak plasma levels occur at 1-2 hours. The drug is mainly metabolised with a half-life of 3-8 hours.

Pharmacodynamics: Primaquine and tafenoquine are 8-aminoquinoline tissue schizonticides which are effective against exoerythrocytic (hepatic) forms of *Plasmodium vivax* and *Plasmodium malariae*. Two weeks of

primaquine are required to eradicate hypnozoites and effect radical cure. Tafenoquine is a new compound with ten times the activity of primaquine as a hypnozoiticide. Treatment with either drug is inappropriate if the patient is liable to re-infection e.g. still living in an endemic area.

Toxicity: The main risk with primaquine is that of haemolysis which may be severe, especially in patients with glucose-6-phosphate dehydrogenase deficiency.

CHLORPROGUANIL(80 MG)+DAPSONE(100 MG), PROGUANIL(100 MG)+ATOVAQUONE(250 MG)

Pharmacokinetics: Proguanil and chlorproguanil are slowly but adequately absorbed after oral administration. Their peak plasma level is attained in about 5 hours and their elimination half-life is about 16 hours. Dapsone is a sulphone with pharmacological properties similar to the sulphonamides (e.g. see sulfadoxine above). Atovaquone has variable poor absorption which is enhanced by a fatty meal. Its elimination half-life is about 60 hours.

Pharmacodynamics: These synergistic combination preparations have been designed to replace sulfadoxine-pyrimethamine in the fight against multidrug resistant *Plasmodium falciparum,* in view of increasingly widespread resistance to S-P[14]. Chlorproguanil and proguanil preferentially inhibit the parasite dihydrofolate reductase. Dapsone is a sulphone which inhibits folic acid synthesis. Atovaquone inhibits Plasmodial mitochondrial respiration.

Toxicity: These preparations may cause anorexia, nausea, vomiting, diarrhoea, abdominal pain, fever, headache, pruritus, rash, dizziness, urticaria and blood disorders.

IRAB (NEEM LEAF EXTRACT)

Extracts from leaves of the neem tree (*Azadirachta indica* A. Juss), known locally as 'dogonyaro', have been used for centuries in the treatment of malaria. An acetone-water extract of neem leaves has been shown to block maturation of malarial parasites beyond the ring stage[15]. This extract also blocks cytoadhesion of infected erythrocytes to endothelium, a key mechanism in the pathogenesis of severe *Plasmodium falciparum* malaria[16]. **Pharmacokinetic** studies of the extract have not yet been undertaken. The demonstrated antimalarial efficacy and a notable lack of toxicity indicate the need for clinical trials to compare irab with more established antimalarials such as quinine and the artemisinins, particularly in severe malaria and cerebral malaria, and also as part of combination chemotherapy.

TREATMENT OF MALARIA

Although confirmation of the diagnosis (by microscopy of stained thin and thick blood films) is important[17], it is equally important not to delay effective drug treatment for malaria, especially in patients with a relative lack of immunity (e.g. during pregnancy, at the extremes of age, after prolonged absence from a malaria-endemic environment) and a lack of protective factors such as a heterozygote sickle genotype. In such patients, delaying effective treatment after the initial attack increases the risk of serious complications and fatality. Deciding on effective treatment depends on the species of malaria parasite and local patterns of drug resistance. Drug intolerance by the host should also be taken into account e.g. chloroquine pruritus, and avoiding potentially teratogenic drugs such as mefloquine, artemisinins and halofantrine during the first trimester of pregnancy.

Plasmodia vivax, ovale and *malariae* remain generally sensitive to chloroquine, responding to 25 mg base per kg of body weight over 36 - 48 hours[18]. However chloroquine-resistant *Plasmodium vivax* has been reported

from Oceania[19]. For patients who leave the malaria-endemic zone, a two-week course of primaquine is required to eradicate hypnozoites of *P. vivax* and *P. ovale*. Primaquine is contraindicated in patients with severe variants of glucose-6-phosphate dehydrogenase deficiency. Emerging human infections with the macaque malaria parasite *Plasmodium knowlesi* are also sensitive to chloroquine and primaquine[20].

In a few areas of the world (such as North Africa and the Middle East) *Plasmodium falciparum* remains sensitive to chloroquine. Elsewhere there is a crisis as unaffordability of effective combination chemotherapy such as co-artemether, and continuing use of cheaper drugs to which the parasite is resistant (mainly chloroquine and S-P), has led to a two-fold to 11-fold increase in child mortality[21, 22] which Attaran et al[23] condemns as "medical malpractice", and Yamey[24,25] as "incompetence" on the part of global health agencies. Thus cost remains a barrier to the effective utilisation of the expanding therapeutic armamentarium against *Plasmodium falciparum* which has been described above.

Drug resistance arises from widespread indiscriminate drug use and hence applies mainly to the cheaper, less toxic drugs, namely chloroquine and S-P. In addition, resistance to mefloquine has been reported from Southeast Asia, Africa and South America, and resistance to quinine from Thailand and Vietnam. Hence combination chemotherapy is now advised for the routine treatment of *Plasmodium falciparum* malaria[26-28], especially in those susceptible to severe complications, both to combat drug-resistant parasites and to forestall the *de novo* development of resistance to drugs such as artemisinin derivatives (resistance to which has not been reported so far).

Combining drugs involves choosing drugs with differing modes of action (to achieve synergy) and differing side effect profiles to avert synergistic toxicity. For example combining drugs with cardiotoxic potential such as halofantrine, quinine, mefloquine, chloroquine or amodiaquine may be fatal. Examples of useful combinations (with efficacy depending on degree of parasite resistance to the component drugs) include chloroquine plus doxycycline, S-P plus mefloquine, quinine plus tetracycline[28], artesunate plus mefloquine[26], mefloquine plus doxycycline, artesunate plus doxycycline and co-artemether (artemether plus lumefantrine)[12,29,30]. Chloroquine plus S-P should no longer be used since parasite resistance to both components is common.

There is anecdotal evidence that irab (acetone-water neem leaf extract) is effective against multidrug resistant *Plasmodium falciparum* prevalent in our environment[31]. Supporting this claim are the *in vitro* evidence of efficacy[15,16] and the fact that neem leaf extracts traditionally known as 'dogonyaro' have been used to treat malaria for centuries.

Patients with multidrug-resistant malaria, and who have acquired or innate immunity, may improve, in spite of, rather than because of, chloroquine given to them. This should not be misconstrued as implying that chloroquine is effective and still indicated for routine use in the treatment of malaria. Indeed continued use of chloroquine as a first-line drug only serves to maintain the population of resistant parasites, while discontinuing routine use of chloroquine for *Plasmodium falciparum* infections would encourage reversion of resistance in the long term.

Chloroquine resistance is mediated by a P-glycoprotein drug efflux pump. Pouliot et al[32] found ivermectin to effectively reverse the multidrug resistance phenotype of neoplastic cells which is associated with the same P-glycoprotein. Ivermectin was more effective and less toxic than other resistance-reversing agents such as verapamil and cyclosporin A. This suggests that ivermectin may also be useful in

combating multidrug resistant *Plasmodium falciparum* malaria, for which P-glycoprotein-drug efflux pump inhibitors are effective *in vitro*[33]. However, Van Schalkwyk et al[34] have found that ivermectin does not potentiate chloroquine accumulation in a chloroquine-resistant strain of *Plasmodium falciparum*.

Childhood And Pregnancy

Primaquine is contraindicated in pregnancy and for neonates because of the risk of haemolysis. Chloroquine, S-P and quinine are safe in pregnancy[35]. However there is a risk of kernicterus from sulfadoxine given in the third trimester. Mefloquine and artemisinins are considered safe in the second and third trimesters. Antimalarials are generally safe during breast feeding, except for primaquine and halofantrine, for which data are lacking. Caution should be exercised with mefloquine and quinine as these may cause vomiting in infants. Prompt treatment to reduce morbidity and mortality is particularly important in young children who may well not yet have acquired sufficient immunity to resist the infection[36].

Ancillary And Supportive Treatments For Severe Malaria

Although excessive pyrexia is undesirable, and hence should be controlled (preferably by non-drug manoeuvres such as a fan and tepid sponging), there is ample evidence that fever is an important part of the protective response against infection, and hence should not be abolished by excessive prescription of antipyretics. Indeed routine prescription of antipyretics should not be the norm in the treatment of uncomplicated malaria[37-41].

Maintaining fluid balance in severe malaria may be difficult, with a tendency both to fluid overload and pulmonary oedema as well as to dehydration and shock. One should aim to maintain the central venous pressure at 5 cm of water. The quinolines (including quinine, mefloquine, halofantrine, chloroquine, amodiaquine) exacerbate postural hypotension in malaria and so patients should be kept lying flat.

Hypoglycaemia is a risk, especially after quinine and quinidine: hence after rehydration patients should receive 5-10% glucose infusion and extra bolus glucose infusion if required[42-44].

If patients deteriorate then a complicating bacterial infection should be considered, blood cultures taken and a broad spectrum antibacterial agent started[45]. If consciousness is impaired then cerebrospinal fluid should be examined to exclude meningitis. Acute renal failure requires dialysis or haemofiltration[46]. Convulsions should be managed with intravenous diazepam.

Blood transfusion may be considered if the haemoglobin concentration drops below 5 g/dl, especially if there are signs of respiratory distress[47]. Antimalarial chemotherapy should be changed if the parasite count does not fall by at least 75% by 48 hours after treatment starts. There is evidence to support the use of exchange transfusion for life-threatening parasitaemia exceeding about 10% of erythrocytes infected[48,49].

Failure Of Therapeutic Response

Apart from the malaria parasites being resistant to the antimalarial drugs used, there may be other reasons for therapeutic failure. Malaria may be the wrong diagnosis: the astute clinician should always be alert to this possibility. On the other hand malaria may be a correct diagnosis but there may be another coincident infection also needing treatment. Concurrent bacterial infection is not uncommon[45]. Indeed the continued reporting of (dying, pyknotic) malaria parasites on blood films should not deceive the clinician into believing the patient has inadequately treated malaria.

One of the most common reasons for therapeutic failure in general is poor compliance i.e. failure to take the prescribed course of medication. There are a wide variety of reasons for poor compliance ranging from illegible or

misplaced prescription charts to intolerable side effects or inability to afford the drugs.

Fake or substandard drugs may also account for therapeutic failure. This possibility should always be considered in our environment when patients fail to improve in spite of apparently good compliance with prescribed treatment. Asking patients the source of their drugs helps to confirm the likely quality and reliability of the drugs.

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